DESCRIPTION

PYRIDINYLPYRAZOLOPYRIMIDINONE DERIVATIVES AS PDE 7 INHIBITORS

Technical Field

The present invention relates to pyridinylpyrazolopyrimidinone compounds, pharmaceutically acceptable salts and solvates thereof, having selective PDE 7 (phosphodiesterase VII) inhibiting effect. These compounds are effective compounds for treating various kinds of disease such as allergic disease, inflammatory disease and immunologic disease.

Background Art

A cyclic AMP (cAMP) or cyclic GMP (cGMP), which is an intracellular second messenger substance, is decomposed and inactivated by phosphodiesterase (PDE 1 to PDE 11). The PDE 7 selectively decomposes cAMP, and is characterized as an enzyme not decomposed by rolipram. Rolipram is a selective inhibitor of PDE 4 which decomposes cAMP.

It is suggested that PDE 7 plays an important role for activating T cells (Beavo, et al., *Science*, 283, 848 (1999)), and well known that activating of T-cell is concerned with the exacerbation of allergic disease, inflammatory disease or immunologic disease. These diseases are for example bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease, allergic rhinitis, psoriasis, atopic dermatitis, conjunctivitis, osteoarthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, hepatitis, pancreatitis, encephalomyelitis, septicemia, Crohn's disease, rejection for organ transplantation, graft versus host disease (GVH disease), and restenosis after angioplasty. [*J. Allergy Clin. Immunol.*, 2000 Nov; 106(5 Suppl.): S221-6; *Am. J. Respir. Crit. Care Med.*, 1996 Feb; 153(2): 629-32; *Am. J. Respir. Crit. Care Med.*, 1999 Nov; 160(5 Pt 2): S33-7; *Clin. Exp. Allergy*, 2000 Feb; 30(2): 242-54; *Hosp. Med.*, 1998 Jul; 59(7): 530-3; *Int. Arch. Allergy Immunol.*, 1998 Mar; 115(3): 179-90; *J. Immunol.*, 1991

Feb 15; 146(4): 1169-74; *Osteoarthritis Cartilage*, 1999 Jul; 7(4): 401-2; *Rheum. Dis. Clin. North Am.*, 2001 May; 27(2): 317-34; *J. Autoimmun.*, 2001 May; 16(3): 187-92; *Curr. Rheumatol. Rep.*, 2000 Feb; 2(1): 24-31; *Trends Immunol.*, 2001 Jan; 22(1): 21-6; *Curr. Opin. Immunol.*, 200 Aug; 12(4): 403-8; *Diabetes Care*, 2001 Sep; 24(9): 1661-7; *J. Neuroimmunol.*, 2000 Nov 1; 111(1-2): 224-8; *Curr. Opin. Immunol.*, 1997 Dec; 9(6): 793-9; *JAMA*, 1999 Sep 15; 282(11):1076-82; *Semin. Cancer Biol.*, 1996 Apr; 7(2): 57-64; *J. Interferon Cytokine Res.*, 2001 Apr; 21(4): 219-21].

Therefore, it is considered that a compound having PDE 7 inhibiting effect is useful for treating various kinds of disease such as allergic disease, inflammatory disease or immunologic disease concerned with T cells.

There has been proposed many compounds selectively inhibit PDE 7. These are for example, imidazopyridine derivatives (International Patent Publication WO 01/34601), dihydropurine derivatives (International Patent Publication WO 00/68203), pyrrole derivatives (International Patent Publication WO 01/32618), benzothiopyranoimidazolone derivatives (DE Patent 19950647), heterocyclic compounds (International Patent Publications WO 02/88080; 02/87513), quinazoline and pyridopyrimidine derivatives (International Patent Publication WO 02/102315), spiro tricyclic compounds (International Patent Publication WO 02/74754), thiazole and oxathiazole derivatives (International Patent Publication WO 02/28847), sulfonamide derivatives (International Patent Publication WO 01/98274), heterobiarylsulfonamide derivatives (International Patent Publication WO 01/74786), dihydroisoquinoline derivatives (International Patent Publication WO 02/40450), guanine derivatives (*Bioorg. Med. Chem. Lett.*, 11(2001), 1081), benzothiadiazine derivatives (*J. Med. Chem.*, 43(2000), 683) and benzothienothiadiazine derivatives (*Eur. J. Med. Chem.*, 36(2001), 333). However, no curative medicines having PDE 7 inhibiting effect as main pharmacological mechanism have developed up to now.

Though some pyrazolopyrimidinone derivatives as cGMP specified PDE inhibitor have been known (For examples: EP 463756; EP 526004; EP 349239;

EP 636626; EP 995751; and Japanese Patent Publication No. Hei8-25384), there is no suggestion that these compounds have PDE 7 inhibiting effect.

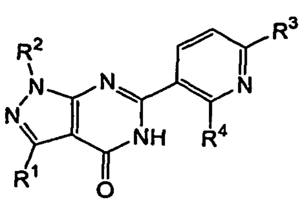
Therefore, the purpose of the present invention is to provide novel compounds having PDE 7 inhibiting effect, and PDE 7 inhibiting composition containing the same as an active ingredient.

The compounds of the present invention inhibit PDE 7 selectively, and therefore, enhance cellular cAMP level. Consequently, the compounds of the present invention are useful for treating various kinds of disease such as allergic disease, inflammatory disease or immunologic disease. For example, the compounds of the present invention are useful for treating or preventing the diseases such as bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease, allergic rhinitis, psoriasis, atopic dermatitis, conjunctivitis, osteoarthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, hepatitis, pancreatitis, encephalomyelitis, septicemia, Crohn's disease, rejection for organ transplantation, GVH disease, restenosis after angioplasty.

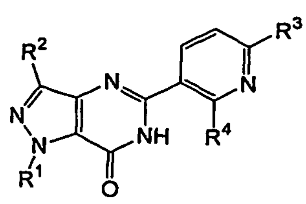
Disclosure of Invention

Through extensive investigations of researching compounds having the capabilities of inhibiting PDE 7, the present inventors discovered that the compounds having pyridinylpyrazolopyrimidinone skeleton in the molecular represented by the formula (IA) or (IB) mentioned below possess potent and selective PDE 7 inhibiting effect, and therefore, completed the present invention.

Accordingly, as one aspect of the present invention, it is provided pyridinylpyrazolopyrimidinone compounds represented by the following formula (IA) or (IB):



(IA)



(IB)

wherein:

R^1 is substituted or unsubsituted C_3-C_8 cycloalkyl group or tert-butyl group;

R^2 is a hydrogen atom or C_1-C_3 alkyl group;

R^3 is a group: $-NR^5R^6$, $-C(=O)R^7$ or $-S(O)_{0-2}R^8$;

R^4 is a hydrogen atom or C_1-C_3 alkoxy group which is unsubstututed or substituted by one or more fluorine atom(s);

R^5 and R^6 are, same or different from each other, a hydrogen atom, substituted or unsubsituted C_1-C_6 alkyl group, substituted or unsubsituted acyl group, substituted or unsubsituted heterocycloalkyl group, and substituted or unsubsituted heterocycloalkyl ring is formed with nitrogen atom which is binding R^5 and R^6;

R^7 is a group: $-OR^9$ or $-NR^5R^6$;

R^8 is a hydrogen atom, a halogen atom, a group: $-NR^5R^6$, substituted or unsubsituted C_1-C_6 alkyl group, or substituted or unsubsituted aryl group;

R^9 is a hydrogen atom or substituted or unsubsituted C_1-C_6 alkyl group;

or pharmaceutically acceptable salts or solvates thereof.

Still another aspect of the present invention, it is provided PDE 7 inhibiting composition containing the pyridinylpyrazolopyrimidinone compounds mentioned above, or pharmaceutically acceptable salts or solvates thereof as an active ingredient.

Best Mode for Carrying Out the Invention

The present invention will now be explained more specifically as following.

The term "C_1-C_3 alkyl group" of the present invention includes a straight or branched-chained alkyl group having 1 to 3 carbon atoms, such as methyl, ethyl and propyl group, and the term "C_1-C_6 alkyl group" of the present invention means a straight or branched-chained alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl and hexyl group. The term "C_3-C_8 cycloalkyl group" of the present invention includes

a cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl.

The term "heterocycloalkyl group" is 3 to 7 membered heterocyclic group containing the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen or sulfur atom(s), and examples may include pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl, tetrahydrofuryl, tetrahydropyranyl, morpholinyl and azetidinyl.

The term "C_1-C_3 alkoxy group" means alkoxy group having 1 to 3 carbon atoms and examples include methoxy, ethoxy and propoxy. The term "acyl group" means acyl group having 1 to 8 carbon atoms, and examples include formyl, acetyl, propionyl, butanoyl, pentanoyl, benzoyl and toluoyl. The "halogen atom" includes fluorine, chlorine, bromine and iodine.

The term "aryl group" is phenyl, naphthyl, biphenyl group which is consisted by 6 to 12 carbon atoms, and the term "heteroaryl group" is 5 to 7 membered monocyclic or polycyclic group thereof containing 2 to 8 carbon atoms and the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen, sulfur atom(s). The examples include pyrrole, furyl, thienyl, imidazolyl, thiazolyl, pyrazinyl, indolyl, quinolinyl, isoquinolinyl, tetrazolyl, pyridinyl, pyrazolyl pyridazinyl and pyrimidinyl.

Examples of suitable substituent of "substituted or unsubstituted C_1-C_6 alkyl group" include hydroxyl group and halogen atom, and examples of suitable substituent of "substituted or unsubstituted acyl group" include halogen atom and nitro group. Further, examples of suitable substituent of "substituted or unsubstituted aryl group" include C_1-C_3 alkyl, halogen atom, amino group, acyl group, amide group, hydroxyl group, acylamino group, carboxyl group and sulfonyl group. Examples of suitable substituent of "substituted or unsubstituted C_3-C_8 cycloalkyl group" is C_1-C_3 alkyl, hydroxyl group and oxo group, and examples of suitable substituent of "substituted or unsubstituted heterocycloalkyl group" may include carboxy group, acyl group, alkoxy group, amino group, alkylamino group, acylamino group, hydroxyl group, oxo group, ethylenedioxy group, methyl group, ethyl group and hydroxyethyl group.

Preferable compounds of the formula (IA) and (IB) of the present invention include the compounds wherein R^1 is cyclohexyl group or cycloheptyl group; R^2 is methyl group; R^3 is the group $-NR^5R^6$ or $-S(O)_{0-2}R^8$; and R^4 is methoxy or ethoxy group.

The compounds of the formula (IA) and (IB) of the present invention may exist in the tautomeric mixtures, the tautomeric isomers *per se*, and the mixture thereof. Furthermore, the radiolabelled compounds of the formula (IA) and (IB) shall be included within the scope of the compounds of the present invention.

The compounds of the present invention may contain one or more asymmetric carbon atom and therefore, the compounds of the present invention may exist as optically isomer of (R)-form or (S)-form, racemic forms, as well as diastereomers. Further, the compounds of the present invention may exist as geometrical isomer such as (Z)-form or (E)-form due to the double bond in the substituent. Therefore, the compounds of the present invention should include these isomers *per se* as well as the isomeric mixtures thereof.

The compounds of the present invention may form acid additional salt thereof with various acids. Examples of the acid additional salt include the salts with inorganic acid such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid and phosphoric acid; salts with organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, benzoic acid, picric acid, methanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, trichloroacetic acid, trifluoroacetic acid, asparaginic acid and glutamic acid.

The compounds of the present invention may form pharmaceutically acceptable metal salts by treating with various kinds of metal, especially alkali metal or alkali earth metal. These salts may include sodium salt, potassium salt and calcium salt. Further, the compounds of the present invention may include hydrate or solvate with water, ethanol or isopropanol, and polymorphisms thereof.

The following compounds are preferable pyridinylpyrazolopyrimidinone compounds of the formula (IA) or (IB).

1-cyclohexyl-5-{2-methoxy-6-[(4-methylphenyl)sulfanyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-{2-methoxy-6-[(4-methylphenyl)sulfonyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

3-cyclohexyl-6-{2-methoxy-6-[(4-methylphenyl)sulfanyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-cyclohexyl-6-{2-methoxy-6-[(4-methylphenyl)sulfonyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclohexyl-5-[2-methoxy-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-[2-methoxy-6-(4-morpholinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-[2-methoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-[6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-[2-methoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-[6-(4-hydroxy-1-piperidinyl)-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-{2-methoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-cyclohexyl-5-{6-[4-(dimethylamino)-1-piperidinyl-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

6-[6-(4-amino-1-piperidinyl)-2-methoxy-3-pyridinyl]-1-cyclohexyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

N-{1-[5-(1-cyclohexyl-3-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]-pyrimidin-5-yl)-6-methoxy-2-pyridinyl]-4-piperidinyl}acetamide;

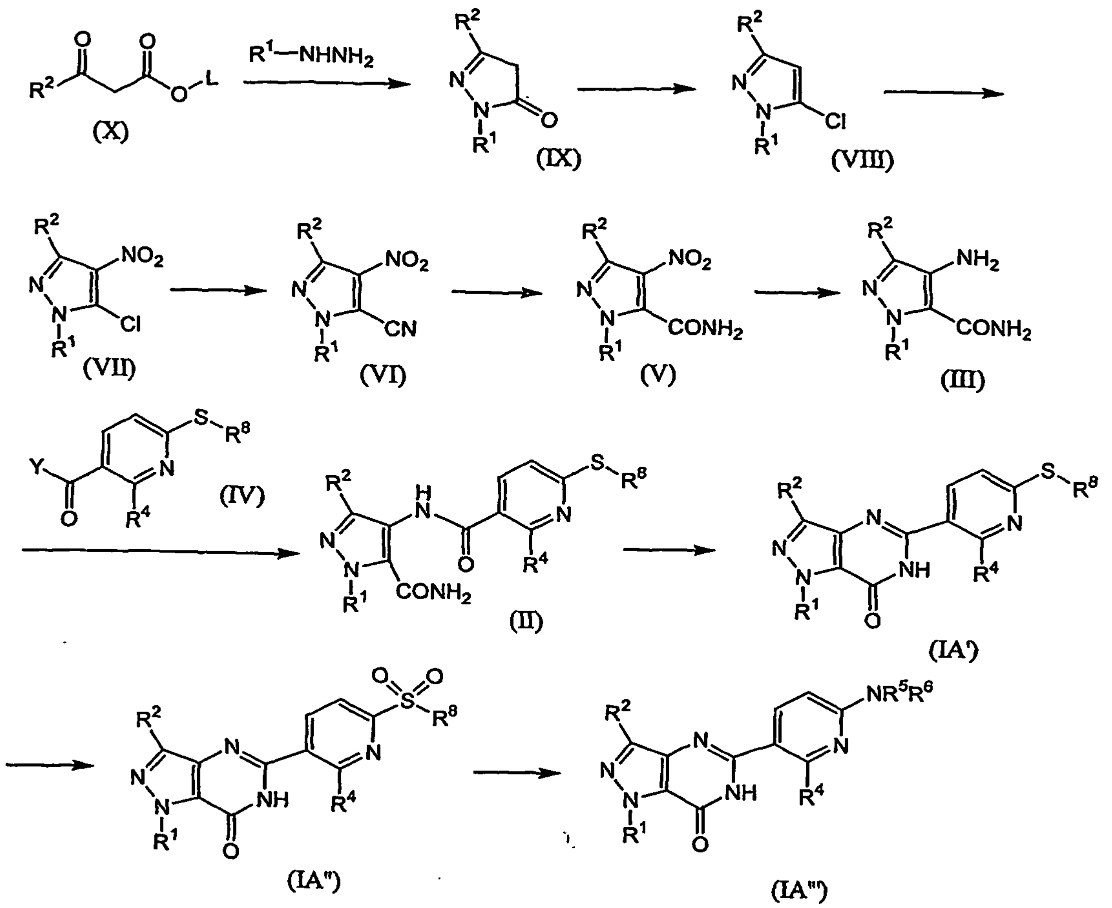
1-cyclohexyl-5-(2-methoxy-3-pyridinyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

3-cyclohexyl-6-[6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methoxy-3-

pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; 3-cyclohexyl-6-[2-methoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; 3-cyclohexyl-6-[6-(4-hydroxy-1-piperidinyl)-2-methoxy-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; 3-cyclohexyl-6-(2-methoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl)-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; 3-cyclohexyl-6-{6-[4-(dimethylamino)-1-piperidinyl]-2-methoxy-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; 6-[6-(4-amino-1-piperidinyl)-2-methoxy-3-pyridinyl]-3-cyclohexyl-1-methyl-1,5-dihydro-4H-pyrazolo[4,3-d]pyrimidin-4-one; N-{1-[5-(3-cyclohexyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-d]-pyrimidin-6-yl)-6-methoxy-2-pyridinyl]-4-piperidinyl}acetamide; 1-cyclohexyl-5-(2-methoxy-3-pyridinyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 3-cyclohexyl-6-[2-methoxy-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-[2-methoxy-6-(4-morpholinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-[2-methoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-[6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methoxy-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-[2-methoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-[6-(4-hydroxy-1-piperidiny)-2-methoxy-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-{2-methoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 3-cyclohexyl-6-{6-[4-(dimethylamino)-1-piperidinyl]-2-methoxy-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; 6-[6-(4-amino-1-piperidinyl)-2-methoxy-3-pyridinyl]-3-cyclohexyl-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

N-{1-[5-(3-cyclohexyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]-pyrimidin-6-yl)-6-methoxy-2-pyridinyl]-4-piperidinyl}acetamide;
3-cyclohexyl-6-(2-methoxy-6-sulfanyl-3-pyridinyl)-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
5-(3-cyclohexyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]-pyrimidin-6-yl)-6-methoxy-2-pyridinesulfonyl chloride;
3-cyclohexyl-6-{2-methoxy-6-[(4-methyl-1,4-diazepan-1-yl)sulfonyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
1-cyclohexyl-5-{2-methoxy-6-[(4-methylphenyl)sulfinyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-{2-ethoxy-6-[(4-methylphenyl)sulfanyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-{2-ethoxy-6-[(4-methylphenyl)sulfonyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexy-5-[2-ethoxy-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-[2-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-[6-(1,4-dioxa-8-azaspiro[4.5]deca-8-yl)-2-ethoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-[2-ethoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-{6-[4-(dimethylamino)-1-piperidinyl]-2-ethoxy-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-{2-ethoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-cyclohexyl-5-[2-ethoxy-6-(4-hydroxy-1-piperidinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compound of the formula (IA) of the present invention can be synthesized by the following methods.



(wherein, R^1, R^2, R^4, R^5, R^6 and R^8 have same meaning mentioned above; L is C_1-C_3 lower alkyl, and Y is hydroxyl group or halogen atom, preferably chlorine atom)

First, the compound (IX) obtained from the compound (X) by reacting with R^1NHNH_2 or salt thereof in accordance with the known method. Namely, the compound (X) is reacted with 1 to 2 equivalent, preferably about 1 equivalent of R^1NHNH_2 or salt thereof in the solvent or absent of the solvent at room temperature to 120°C. The solvent to be used in the reaction is inorganic acid aqueous solution such as hydrochloric acid or sulfuric acid; aromatic carbon hydrate such as benzene or toluene; organic acid such as acetic acid; alcohols such as methanol or ethanol; or the mixture solvent there of. After the reaction is completed, inorganic base aqueous solution such as sodium hydroxide aqueous solution is added to the reaction mixture and the mixture is extracted wit an organic solvent, which is

nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (IX) can be obtained by removal of the solvent. This compound (IX) can be purified by recrystallization, if necessary.

The compound (X) to be used in this reaction can be commercially available or can be easily prepared from known compounds by using common methods. Further, the compound represent by the formula R^1NHNH_2 or salt thereof can also be commercially available or can be easily prepared from known compounds by using common methods (For example: *J. Org. Chem.*, 1981, 46, 5414-5415).

Then, the compound (IX) is converted to the compound (VIII) in accordance with the common method. Namely, the reaction can be conducted by reacting the compound (IX) with 1 to 5 equivalent of halogenate reagent such as phosphorus oxychloride or thionyl chloride in aromatic hydrocarbon solvent such as benzene or toluene, or the absence of the solvent, at room temperature to refluxing temperature of the solvent. After the reaction is completed, the compound (VIII) can be obtained by removal of the solvent.

The obtained compound (VIII) is converted, without further purification, to the compound (VII) by nitration in accordance with the common method. The nitration can be conducted by using nitric acid with sulfuric acid or acetic anhydride at the temperature from -20° to room temperature. After the reaction is completed, the reaction mixture is poured into ice and the resulting precipitate is collected to obtain the purpose compound (VII). This compound (VII) can be purified by recrystallization, if necessary.

Next, the obtained compound (VII) is converted to the compound (VI) in accordance with the common method. Namely, the reaction can be conducted by reacting the compound (VII) with 1 to 3 equivalent metal cyanide such as potassium cyanide or sodium cyanide in a polar solvent such as N,N-dimethylformamide at room temperature to 120°C. After the reaction is completed, water is added to the reaction mixture and the mixture is extracted with an organic solvent, which is nonmiscible solvent with water,

and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (VI) can be obtained by removal of the solvent. This compound (VI) can be purified by chromatography, if necessary.

The obtained compound (VI) is converted to the compound (V) in accordance with the common method. This reaction is hydrolysis reaction of nitrile group converting to the corresponding acid amide group, and various methods are applied. For example, the reaction can be conducted by reacting the compound (VI) with hydrogen peroxide in the presence of base such as sodium hydroxide or potassium carbonate in a solvent at 0°C to the room temperature. The solvent to be used is water, alcohols such as methanol or ethanol, ethers such as 1,4-dioxane or tetrahydrofuran, or the mixture thereof. After the reaction is completed, the reaction mixture is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (V) can be obtained by removal of the solvent. This compound (V) can be purified by recrystallization, if necessary.

Then, the obtained compound (V) is converted to the compound (III) in accordance with the common method. This reaction is reduction of nitro group converting to the corresponding amino group, and various methods are applied. For example, the reaction can be conducted by reacting the compound (V) with 2 to 10 equivalent of tin(II) chloride in the presence of inorganic acid such as hydrochloric acid at 0°C to the refluxing temperature. After the reaction is completed, the reaction mixture is neutralized by inorganic base such as sodium hydroxide, and filtrate by Celite®. The obtained filtrate is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (III) can be obtained by removal of the solvent. This compound (III) can be purified by chromatography, if necessary.

The obtained compound (III) is, then, converted to the compound (II) in accordance with the common method. This reaction can be conducted

by the reaction of the amine compound (III) with carboxylic compound (IV) to obtain the corresponding acid amide compound (II), and various methods are applied. For example, in the case of the compound (IV) in which Y is halogen atom, preferably chlorine atom, the reaction can be conducted by reacting the compound (III) with 1.0 to 1.5 equivalent, preferably 1.2 equivalent of the compound (IV) in the presence of 1 to 5 equivalent, preferably 2.5 equivalent of tertiary amine such as triethylamine, based on the compound (III), and if necessary in the presence of the catalyst such as 4-dimethylaminopyridine. The reaction can be carried out in the presence of inert solvent such as dichloromethane at 0°C to the room temperature.

Furthermore, in the case of the compound (IV) in which Y is hydroxyl group, the reaction can be conducted by reacting the compound (III) with 1.0 to 1.5 equivalent, preferably 1.2 equivalent of the compound (IV) in the presence of 1 to 5 equivalent, preferably 1.2 equivalent of the condensing agent such as 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride, based on the compound (III), and if necessary in the presence of the catalyst such as 4-dimethylaminopyridine in the inert solvent such as dichloromethane.

After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution, then, the solvent is removed to give the purpose compound (II). This compound can be purified by column chromatography, if necessary.

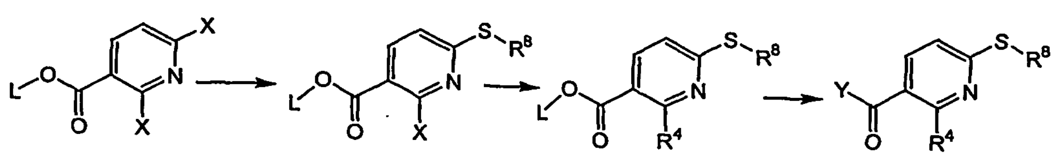
Then, the obtained compound (II) is converted to the compound (IA') by pyrimidine ring formation reaction. This ring formation reaction can be carried out by heating the compound (II) with base such as sodium hydroxide, potassium t-butoxide or potassium carbonate in ethanol/water in the seal tube at 120 to 140°C. Further, the reaction can be carried out in high boiling solvent such as methoxyethanol in the presence of base such as potassium t-butoxide at 120 to 140°C. After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with

water and saturated saline solution. Then, the compound (IA') can be obtained by removal of the solvent. This compound (IA') can be purified by chromatography or recrystallization, if necessary.

The compound (IA'') can be obtained from the obtained compound (IA') by the function group converting reaction with per acid such as m-chloroperbenzoic acid or magnesium mono-peroxyphthalate in chloroform or dichloromethane or chloroform at °C to the room temperature.

Further, the compound (IA''') can be obtained by reacting the compound (IA'') with lithium amide, which is obtained by reacting the amine compound with n-butyllithium. For example, to 2 to 5 equivalent of amine compound based on the compound (IA'') in ethers such as 1,4-dioxan or tertahydrofuran is added by dripping same equivalent of n-butyl lithium to obtain corresponding lithium amide at -78°C to 0°C, and then the compound (IA'') is added to this mixture of lithium amide solution to obtain the compound (IA'''). After the reaction is completed, water is added to the reaction mixture and the mixture is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution, then, the solvent is removed to give the purpose compound (IA''').

The carboxylic compound (IV) to be used in the above reaction can be obtained by the following reaction scheme.



(XIII) (XII) (XI) (IV)

(wherein, L, Y, R^4 and R^6 have same meaning mentioned above; and X is a halogen atom)

Namely, the compound (XII) is obtained from the compound (XIII) in accordance with the known method (e.g., *Chem. Pharm. Bull.*, 48(12), 1847-1853 (2000)). For example, the reaction can be conducted by reacting the compound (XIII) with about 1 equivalent thiol compound such as ethanethiol or benzenethiol in the presence of base such as potassium

t-butoxide, in polar solvent such as N,N-dimethylformamide at the room temperature to -30°C, preferably -30°C. After the reaction is completed, water is added to the reaction mixture and the mixture is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (XII) can be obtained by removal of the solvent. This compound (XII) can be purified by recrystallization, if necessary.

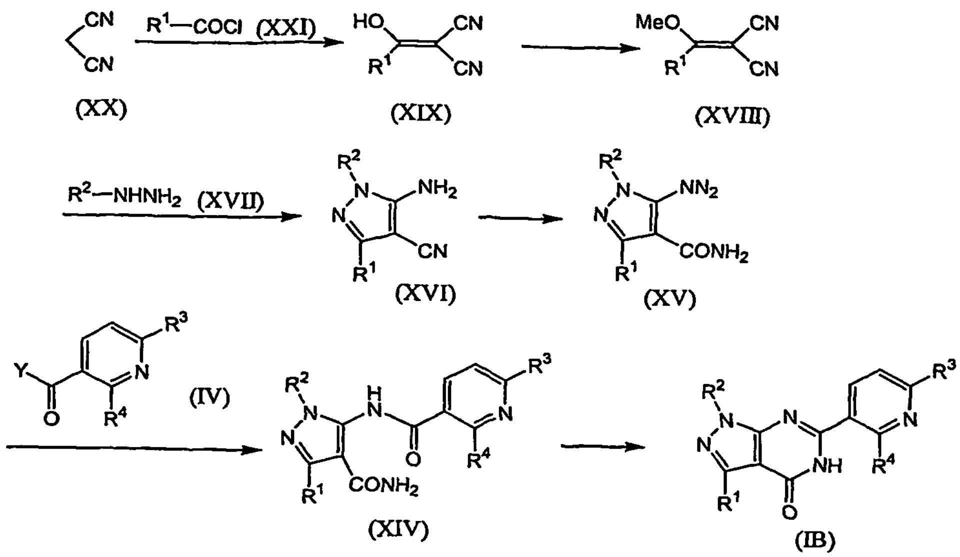
Then, obtained compound (XII) is converted to the compound (XI) in accordance with common method. For example the reaction is conducted by reacting the compound (XII) with small excess of metal alcoholate such as sodium methylate in ethers solvent such as 1,4-dioxan or tetrahydrofuran at the room temperature to refluxing temperature. After the reaction is completed, water is added to the reaction mixture and the mixture is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (XI) can be obtained by removal of the solvent. This compound (XI) can be purified by recrystallization, if necessary.

The obtained compound (XI) is converted to the compound (IV) in accordance with common method. This reaction is hydrolysis reaction of ester compound and various methods are applied. For example the reaction is conducted by reacting the compound (XI) with base such as sodium hydroxide in the alcohol solvent such as methanol or water, as well as a mixture thereof at the room temperature to refluxing temperature. After the reaction is completed, the reaction mixture is condensed and the residue is neutralized to give the compound (IV).

All reaction mentioned above are well known, and the reagents to be used or the reaction conditions to be applied can be easily established in accordance with the standard text book and the examples mentioned later. Further, the other methods or modified methods for obtaining the compound (IA) of the present invention can be easily selected by the person skilled in this field.

The compound of the formula (IB) of the present invention may be

synthesized by the following methods.



(wherein, R^1, R^2, R^3 and R^4 have same meaning mentioned above; and Y is hydroxyl group or halogen atom, preferably chlorine atom)

At the beginning, to carry out the method described above, the compound (XIX) is obtained from the compound (XX) in accordance with the known method (e.g., *J. Chem. Soc, Perkin Trans. I*, 1996, 1545-1552). This method can be conducted by the reaction of the compound (XX) with 1 to 1.5 equivalent of the compound (XXI) based on the compound (XX), in the presence of the 2 to 2.5 equivalent of alkali metal hydride such as sodium hydride and potassium hydride, or tertiary amine such as triethlyamine based on the compound (XX). The reaction can be carried out in an appropriate solvent and these are halogenated hydrocarbons such as dichloromethane; aromatic hydrocarbon such as toluene and benzene; ethers solvent such as diethyl ether tetrahydrofuran; or a mixture of solvent thereof. The reaction temperature is a range from 0°C to the room temperature. After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (XIX) can be obtained by removal of the solvent. This compound (XIX) can be purified by chromatography, if necessary.

Then, the obtained compound (XIX) is converted to the compound (XVIII)

in accordance with the common method (e.g., *J. Chem. Soc, Perkin Trans. I*, 1996, 1545-1552). For example, the reaction can be carried out by the reacting the compound (XIX) with 5 to 10 equivalent of the methylation reagent such as dimethyl sulfate in an appropriate solvent. The solvent to be used in this reaction may include halogenated hydrocarbons such as dichloromethane; aromatic hydrocarbon such as toluene and benzene; ethers solvent such as diethyl ether tetrahydrofuran; or a mixture of solvent thereof, and the reaction temperature is from the room temperature to the refluxing temperature of the solvent. After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (XVIII) can be obtained by removal of the solvent. This compound (XVIII) can be purified by chromatography, if necessary.

Next, the obtained compound (XVIII) is converted to the compound (XVI) in accordance with the common method (e.g., *J. Chem. Soc, Perkin Trans. I*, 1996, 1545-1552). For example, the reaction can be carried out by the reacting the compound (XVIII) with 1 to 1.5 equivalent of the compound XVII) based on the compound (XVIII) in an appropriate solvent. The solvent to be used in this reaction may include halogenated hydrocarbons such as dichloromethane; aromatic hydrocarbon such as toluene and benzene; ethers solvent such as diethyl ether tetrahydrofuran; or a mixture solvent thereof, and the reaction temperature is from the room temperature to the refluxing temperature of the solvent. After the reaction is completed, the solvent is removed to give the compound (XVI). This compound (XVI) can be purified by chromatography, if necessary.

Then, the obtained compound (XVI) is converted to the compound (XV) in accordance with the common method. This reaction is hydrolysis reaction of nitrile group converting to the corresponding acid amide group, and various methods are applied. For example, the reaction can be conducted by treating the compound (XVI) with catalyst such as sulfuric acid or hydrochloric acid in an appropriate solvent at the room temperature to 100°C. The solvent to be used is water, alcohols such as methanol or ethanol,

ethers such as diethyl ether, tetrahydrofuran or dioxane, or the mixture thereof. After the reaction is completed, the pH of reaction mixture is adjusted to alkali side, and the reaction mixture is extracted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (XV) can be obtained by removal of the solvent. This compound (XV) can be purified by recrystallization, if necessary.

The obtained compound (XV) is, then, converted to the compound (XIV) in accordance with the common method. This reaction can be conducted by the reaction of the compound (XV) with compound (IV) to obtain the corresponding acid amide compound (XIV). For example, in the case of the compound (IV) in which Y is halogen atom, preferably chlorine atom, the reaction can be conducted by reacting the compound (XV) with 1.0 to 2.0 equivalent, preferably about 1.4 equivalent of the compound (IV) in the presence of 1 to 5 equivalent, preferably 2.5 equivalent of tertiary amine such as triethylamine, based on the compound (XV), and if necessary in the presence of the catalyst such as 4-dimethylaminopyridine. The reaction can be carried out in the presence of inert solvent such as dichloromethane at 0°C to the room temperature.

Furthermore, in the case of the compound (IV) in which Y is hydroxyl group, the reaction can be conducted by reacting the compound (XV) with 1.0 to 1.5 equivalent, preferably about 1.2 equivalent of the compound (IV) in the presence of 1 to 5 equivalent, preferably about 1.2 equivalent of the condensing agent such as 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide hydrochloride, based on the compound (XV), and if necessary in the presence of the catalyst such as 4-dimethylaminopyridine in the inert solvent such as dichloromethane.

After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution, then, the solvent is removed to give the purpose compound (XIV).

Then, the obtained compound (XIV) is used for the next reaction

without further purification, and is converted to the compound (IB) by pyrimidine ring formation reaction by mean of the known method (e.g., *J. Med. Chem.*, 39 1635-1644(1996)). This ring formation reaction can be carried out by heating the compound (XIV) with base such as sodium hydroxide, potassium t-butoxide or potassium carbonate in ethanol/water in the seal tube at 120 to 140°C. Further, the reaction can be carried out in high boiling solvent such as methoxyethanol in the presence of base such as potassium t-butoxide at 120 to 140°C. After the reaction is completed, the reaction mixture is diluted with an organic solvent, which is nonmiscible solvent with water, and the organic layer is washed sequentially with water and saturated saline solution. Then, the compound (IB) can be obtained by removal of the solvent. This compound (IB) can be purified by chromatography or recrystallization, if necessary.

All reaction mentioned above are well known, and the reagents to be used or the reaction conditions to be applied can be easily established in accordance with the standard text book and the examples mentioned later. Further, the other methods or modified methods for obtaining the compound (IB) of the present invention can be easily selected by the person skilled in this field.

Examples:

The present invention is illustrated in more detail by way of the following Biological Test and Examples, but it is to be noted that the present invention is not limited by those Examples in any way.

The synthesis of the compounds of the present invention and intermediate compounds to be used in the synthesis are illustrated in the Example mentioned later. Further, the physicochemical data and chemical structure of the compounds and intermediate compounds obtained by the Examples are summarized in the Tables mentions later.

The compound numbers in the Examples are identical to those in the Tables.

The PDE 7 (phosphodiesterase VII) inhibiting effect of the compounds

of the present invention obtained in the later mentioned Examples was evaluated by mean of the following Biological Tests.

Biological Test 1:

Methods for evaluating the PDE 7 inhibiting effect

The PDE 7 (phosphodiesterase VII) inhibiting effect of the compounds of the present invention was performed by the following method, which was modified assay method described in *Biochemical. Pharmacol.* 48(6), 1219-1223 (1994).

(1) The active fraction of PDE 7 (phosphodiesterase VII) was obtained. That is, MOLT-4 (obtainable from ATCC as ATCC No. CRL-1582), which was cell line of human acute lymphoblastic lymphoma T cells, was incubated in RPMI1640 culture medium containing 10% fetal bovine serum to obtain 5×10^8 MOLT-4 cells. The cells were collected by centrifugation and suspended with 10mL of buffer solution A [25mM of tris-HCl, 5mM of 2-mercaptoethnol, 2mM of benzamidine, 2mM of EDTA, 0.1mM of 4-(2-aminoethyl)benzensulfonyl hydrochloride; pH 7.5], then homogenized by Polytron® homogenizer. The homogenate were centrifuged under 25,000 × G for 10 minutes at 4°C. The supernatant was separated and thus obtained supernatant was further centrifuged under 100,000 × G for 60 minutes at 4°C, and then filtrated with 0.2μm filter to obtain the soluble fraction.

(2) The obtained soluble fraction was filled in equilibrium HiTrap Q column (5mL × 2) with buffer solution A, and phosphodiesterase fractions were eluted by 300mL of buffer solution A with linear gradient from 0 to 0.8 M NaCl concentration. 5 ml each of 60 eluents were collected, and each eluents were examined for cyclic AMP metabolic activities of phosphodiesterase. The fraction eluting with about 350mM NaCl concentration parts, where metabolic activities were not inactivated by 10μM of rolipram (selective inhibitor for phosphodiesterase IV) and 10μM of milrinone (selective inhibitor for phosphodiesterase III), were collected as storage solution for using to test PDE 7 inhibiting effect.

(3) The tested compound having desired concentration was reacted in the solution of 20mM tris-HCl (pH 7.5), 1mM of $MgCl_2$, 100μM of EDTA, 330μg/mL

of bovine serum albumin, 4μg/mL of 5'-nucleotidase, 0.1μCi of ^{3}H-cAMP (0.064μM of cAMP), 10μM of rolipram in storage solution of PDE 7 for 2 hours at 25°C. After the reaction, suspension of Sephadex®-QAE in 10mM of HEPES-Na (pH 7.0) was added to the reaction mixture, and the mixture was left at rest for 5 minutes. Further, Sephadex®-QAE was added to the obtained supernatant and the mixture was leaved at rest for 5 minutes, then, the radioactivity of the solution was measured.

(4) IC_{50} was calculated as 50% inhibiting concentration of the metabolic activities of phosphodiesterase VII of the tested compound.

PDE 7 inhibiting effect of the each tested compounds:

The following compounds showed no more than 0.1 μM of IC_{50} values. Compounds NO. 16, 17, 18, 20, 21, 22, 25, 26, 27, 28, 29, 32, 33, 36, 37, 43, 44, 47, 48, 49.

Further, the following are PDE 7 inhibiting activities of the tested compounds.

Compound 26: IC_{50} = 0.0026μM;

Compound 32: IC_{50} = 0.0032μM;

As described above, the compounds of the present invention showed significant PDE 7 inhibiting effect.

The compounds of the present invention selectively inhibit PDE 7 and their selectivities are more than 10 times compared to PDE 4 (phosphodiesterase IV), which is similar to the PDE 7. Therefore, it is expected that the side effect of the compounds of the present invention caused by PDE 4 to be less. The selectivity against PDE 4 (phosphodiesterase IV) of the compounds of the present invention was affirmed by means of the following Biological Test.

Biological Test 2:

Methods for evaluating the PDE 4 inhibiting effect

The PDE 4 (phosphodiesterase IV) inhibiting effect of the compounds of the present invention was performed by the following method, which

was modified assay method described in *Biochemical. Pharmacol.* 48(6), 1219-1223 (1994).

(1) The active fraction of PDE 4 (phosphodiesterase IV) was obtained. That is, the livers obtained from three Balb/c mice (male, 12 weeks: obtainable from CLEA Japan, Inc.) were suspended with 30mL of buffer solution B [20mM of bis-tris, 5mM of 2-mercaptoethnol, 2mM of benzamidine, 2mM of EDTA, 0.1mM of 4-(2-aminoethyl)benzensulfonyl hydrochloride, 50mM of sodium acetate; pH 6.5], then homogenized by Polytron® homogenizer. The homogenate were centrifuged under 25,000 × G for 10 minutes at 4°C. The supernatant was separated and thus obtained supernatant was further centrifuged under 100,000 × G for 60 minutes at 4°C, and then filtrated with 0.2μm filter to obtain the soluble fraction.

(2) The obtained soluble fraction was filled in equilibrium DEAE sepharose column (1 × 10cm) with buffer solution B, and phosphodiesterase fractions were eluted by 120mL of buffer solution B with linear gradient from 0.05 to 1M sodium acetate concentration. 5 ml each of 24 eluents were collected, and each eluents were examined for cyclic AMP metabolic activities of phosphodiesterase. The fraction eluting with about 620mM of sosdium acetate concentration parts, where metabolic activities were inactivated by 30μM of rolipram (selective inhibitor for phosphodiesterase IV), were collected as storage solution to test PDE 4 inhibiting effect.

(3) The tested compound having desired concentration was reacted in the solution of 20mM tris-HCl (pH 7.5), 1mM of $MgCl_2$, 100μM of EDTA, 330μg/mL of bovine serum albumin, 4μg/mL of 5'-nucleotidase, 0.1μCi of ^{3}H-cAMP (0.064μM of cAMP), and storage solution of PDE 4 for 2 hours at 25°C. After the reaction, suspension of Sephadex®-QAE in 10mM of HEPES-Na (pH 7.0) was added to the reaction mixture, and the mixture was left at rest for 5 minutes. Further, Sephadex®-QAE was added to the obtained supernatant and the mixture was left at rest for 5 minutes, then, the radioactivity of the solution was measured.

(4) IC_{50} was calculated as 50% inhibiting concentration of the metabolic activities of phosphodiesterase IV of the tested compound.

As the results of the mentioned above Biological Test 2, the IC_{50}

of the compounds of the present invention was more than 10 times weaker than that of PDE 7 inhibiting effect.

The following are PDE 4 inhibiting activities of the tested compounds.

Compound 26: IC_{50} = 1.2μM;

Compound 32: IC_{50} = 0.98μM;

The compounds of the present invention inhibit PDE 7 selectively, and therefore, enhance cellular cAMP level. Consequently, the compounds of the present invention are useful for treating various kinds of disease such as allergic disease, inflammatory disease or immunologic disease. For example, the compounds of the present invention are useful for treating or preventing the diseases such as bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease, allergic rhinitis, psoriasis, atopic dermatitis, conjunctivitis, osteoarthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, hepatitis, pancreatitis, encephalomyelitis, septicemia, Crohn's disease, rejection for organ transplantation, GVH disease, and restenosis after angioplasty.

The compounds of the present invention can be used for preparation of the pharmaceutical composition or PDE 7 inhibitor. As an active ingredient, one or more compounds may be administered in the appropriated formulation. The formulation for oral administration may include for example, capsules, granules, fine granules, syrups, dry syrups or the like; the formulation for parenteral administration may include, for example injectable solution, suppository formulation such as rectal suppository or vaginal suppository, nasal administration such as sprays, or percutaneous absorption formulation such as ointment and tapes, and the like.

The administration dose may vary depending on the various kinds of factors. These factors may be the condition of the patients, the severity of the disease, ages, existence of a complication, as well as formulation. A usual recommended daily dose for oral administration is within the range of 0.1 - 1,000mg/day/adult, preferably 0.1 - 500mg/day/adult, and more

preferably 1 - 100mg/day/adult. In the case of parenteral administration, a usual recommended daily dose is within the range of 1/1000 to1/2 based on dose of oral administration. These doses can be adjusted depending on age, as well as the patient's condition.

The toxicological properties of the compounds of the present invention is low, therefore, the compounds of the present invention is expected to have high safety margin.

Manufacturing Examples and Examples:

The synthesis of the compounds of the present invention is illustrated in the following Examples.

The physicochemical data and chemical structure of the compounds are summarized in the Tables mentions later. The compound numbers in the Examples are identical to those in the Tables.

Example 1:

2-Cyclohexyl-5-methyl-2,4-dihydro-3H-pyrazol-3-one

A mixture solution of 14.5mL(0.134mol) of methyl acetoacetate and 20.2g (0.134mol) of cyclohexylhydrazine hydrochloride was stirred for 2 hours at 120°C, and the mixture was cooled. Then, the reaction mixture was neutralized with 30mL of 4M-sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting residue was treated with hexane. The resulting precipitate was collected to give 19.0g (79%) of the titled compound.

Example 2:

5-Chloro-1-cyclohexyl-3-methyl-4-nitro-1H-pyrazole

To 9.3g (51.6mmol) of the compound obtained by the Example 1 was added 10mL (107mmol) of phosphorus oxychloride, and the mixture was stirred for 10 hours at 120°C. The reaction mixture was cooled to the room temperature and excess phosphorus oxychloride was removed off under reduced

pressure. The resulting residue was dissolved in 45mL of acetic anhydride, and to this mixture was gradually added by dripping 9mL of fuming nitric acid under ice cooling and the mixture was stirred for 2 hours at the same temperature. Then, the mixture was poured into ice and the resulting precipitate was collected and dissolved in dichloromethane. The organic layer was washed with sodium hydrogen carbonate aqueous solution, water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was recrystallized from hexane to give 6.28g (50%) of the title compound. Further, the filtrate was removed off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 6/1) to give 4.21g (33%) of the title compound.

Example 3:

1-Cyclohexyl-3-methyl-4-nitro-1H-pyrazole-5-carbonitrile

To a solution of 10.3g (42.2mmol) of the compound obtained in the Example 2 in 90mL of N,N-dimethylformamide was added 4.2g (84.9 mmol) of sodium cyanide, and the mixture was stirred for 1.5 hours at 80°C. After the reaction mixture was cooled to the room temperature, the reaction mixture was treated with water and extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 6/1) to give 9.18g (93%) of the title compound.

Example 4:

4-Amino-1-cyclohexyl-3-methyl-1H-pyrazole-5-carbonitrile

To a solution of 1.0g (4.27mmol) of the compound obtained in the Example 3 in 10mL of methanol and 10mL of concentrated hydrochloric acid was added 1.2g (21.4mmol) of iron powder, and the mixture was refluxed for 2 hours. Then, the reaction mixture was cooled to the room temperature, neutralized by sodium hydrogen carbonate aqueous solution, and filtrated

with Celite®. The filtrate was extracted with dichloromethane, and the organic layer was washed with water and saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 7/1) to give 0.75g (87%) of the title compound.

Example 5:

1-Cyclohexyl-3-methyl-4-nitro-1H-pyrazole-5-carboxamide

To a solution of 9.0g (38.5mmol) of the compound obtained in the Example 3 in 25mL of methanol were added 12mL of 30% hydrogen peroxide aqueous solution and 30mL of 3M-sodium hydroxide aqueous solution, and the mixture was stirred at room temperature for 1.5 hours. Then, water was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed to give 7.8g (80%) of the title compound.

Example 6:

4-Amino-1-cyclohexyl-3-methyl-1H-pyrazole-5-carboxamide

To a suspension of 7.7g (30.6mmol) of the compound obtained in the Example 5 in 180mL of concentrated hydrochloric acid was added 27.6g (122mmol) of zinc chloride dihydrate, and the mixture was stirred for 1.5 hours at 80°C. Then, the reaction mixture was cooled to the room temperature and neutralized with sodium hydroxide aqueous solution. After filtrated by Celite®, the filtrate was extracted with dichloromethane, and the organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: ethyl acetate) to give 6.05g (89%) of the title compound.

Example 7:

2-Methoxy-6-[(4-methylphenyl)sulfanyl]nicotinic acid

To a suspension of 9.25g (31.96mmol) of methyl 2-methoxy-6-(4-methyl benzylthio)pyridine-3-carboxylate in 80mL of methanol was added 38.36mL (38.36mmol) of 1N-sodium hydroxide aqueous solution, and the mixture was refluxed for 1 hour. After the reaction mixture was cooled to the room temperature, the solvent was removed under reduced pressure and the residue was diluted with water. Then 2N-HCl was added to the solution and the resultant precipitate was collected to obtain 8.92g (quantitative) of the title compound.

Example 8:

1-Cyclohexyl-5-{2-methoxy-6-[(4-methylpheny)sulfanyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a suspension of 3.03g (11mmol) of the compound obtained in the Example 7 in 30mL of 1,2-dichloroethane was added 1.60mL (22mmol) of thionyl chloride, and the mixture was refluxed for 1.5 hours. After the reaction mixture was cooled to the room temperature, the solvent was removed under reduced pressure to give the corresponding acid chloride.

To a solution of 2.22g (10mmol) of the compound obtained in the Example 6 in 30mL of chloroform were added above acid chloride in 20mL of chloroform, 3.48mL (25mmol) of triethylamine and 5mg of dimethyl-aminopyridine, and the mixture was stirred over night. Then, water was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the corresponding amide compound as pale yellowish solid.

The obtained amide compound was suspended in 50mL of methoxyethanol and to this mixture was added 2.81g (25mmol) of potassium tert-butoxide and the mixture was stirred for 40 minutes at 130°C. After the reaction mixture was cooled to the room temperature, the solvent was removed under reduced pressure. The resulting residue was diluted with water and 26mL of 1N-HCl was added. The mixture was extracted with chloroform and the organic layer was dried over anhydrous sodium sulfate. The solvent was

removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3/1) to give 3.64g (79%) of the title compound.

Example 9:

1-Cyclohexyl-5-{2-methoxy-6-[(4-methylphenyl)sulfonyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a solution of 1.5g (3.25mmol) of the compound obtained in the Example 8 in 40mL of dichloromethane was added 1.54g (7.15mmol) of m-chloroperbenzoic acid at 0°C, and the mixture was stirred for 2 hours. Then, saturated sodium hydrogen carbonate aqueous solution was added to the mixture and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1.75g (quantitative) of the title compound. This compound was used for the next reaction without further purification.

Example 10:

2-[Cyclohexyl(hydroxyl)methylene]malononitrile

To a solution of 3.96g (0.06mol) of malononitrile in 60mL of tetrahydrofuran was added 4.8g (60% dispersion in mineral oil; 0.12mol) of sodium hydride in 4 separate times at 0°C, and the mixture was stirred for 30 minutes at the same temperature. Then, to this mixture was added by dripping cyclohexanecarboxylic chloride and the mixture was stirred for 30 minutes at room temperature. 150mL of 1M-HCl was added slowly to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduces pressure. The resulting residue was recrystallized from diisopropyl ether to give 8.16g (77%) of the title compound.

Example 11:

2-[Cyclohexyl(methoxy)methylene]malononitrile

To a mixture of 2.64g (15mmol) of the compound obtained in the Example

10 in 24mL of 1,4-dioxane and 4mL of water was added 10g of sodium hydrogen carbonate and 10mL of dimethyl sulfate was added by dripping for 5 minutes to this mixture. After the mixture was heated for 2.5 hours at 85°C, the reaction mixture was cooled to the room temperature and water was added to the reaction mixture. The mixture was extracted with diethyl ether and the extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3/1) to give 2.35g (82%) of the title compound.

Example 12-1:

5-Amino-3-cyclohexyl-1-methyl-1H-pyrazole-4-carbonitrile

To a solution of 2.3g (12.1mmol) of the compound obtained in the Example 11 in 20mL of ethanol was added 0.643mL (12.1mmol) of methylhydrazine, and the mixture was refluxed for 5 hours. After the mixture was cooled to the room temperature, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 50/1) to give 1.48g (60%) of the title compound.

Example 12-2:

5-Amino-3-cyclohexyl-1-methyl-1H-pyrazole-4-carbonitrile

To a solution of 17.2g (260mmol) of malononitrile in 260mL of tetrahydrofuran was added slowly to 20.8g (60% dispersion in mineral oil; 520mmol) of sodium hydride at 0°C, then, to this mixture was added by dripping 35mL (260mmol) of cyclohexanecarbonyl chloride at the same temperature and the mixture was stirred for 1.5 hours at room temperature. Then, 30mL (312mmol) of dimethyl sulfate was added to the reaction mixture and the mixture was refluxed for 3 hours. Then, 17.4mL (125mmol) of triethylamine and 13.8mL (260mmol) of methylhydrazine were added to the reaction mixture under ice cooling and the mixture was refluxed for 1 hour. After the mixture was cooled to the room temperature, the solvent was removed under reduce pressure. Water was added to the residue and

the mixture was extracted with ethyl acetate and the organic layer was washed with water, and saturated saline solution, then, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 to 20/1). The obtained crude crystalline was further purified by recrystallization (hexane-ethyl acetate) to give 20.7g (39%) of the title compound. The filtrate was further purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2:1) to give 11.3g (21%) of the title compound.

Example 13:

5-Amino-3-cyclohexyl-1-methyl-1H-pyrazole-4-carboxamide

75mL of concentrated. HCl was added to 25.3g (124mmol) of the compound obtained in the Example 12, and the mixture was stirred for 15 minutes at room temperature and for 1 hour at 60°C. Then, the reaction mixture was poured into ice, neutralized by sodium hydroxide aqueous solution and extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was recrystallized from ethyl acetate to give 20.2g (73%) of the title compound.

Example 14:

3-Cyclohexyl-6-{2-methoxy-6-[(4-methylphenyl)sulfanyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a suspension of 2.70g (9.81mmol) of the compound obtained in the Example 7 in 30mL of 1,2-dichloroethane was added 1.43mL (19.6mmol) of thionyl chloride, and the mixture was refluxed for 2 hours. Then, the reaction mixture was cooled to the room temperature and the solvent was removed under reduced pressure to give the corresponding acid chloride as yellowish solid.

To the solution of the obtained acid chloride in 30mL of pyridine were added 1.82g (8.17mmol) of the compound obtained in the Example 13

and 5mg of dimethylaminopyridine, and the mixture was stirred for 20 hours at room temperature. Then, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the corresponding amide compound as pale yellowish solid.

The obtained amide compound was suspended in 50mL of methoxyethanol and to this suspension was added 2.30g (20.4mmol) of potassium t-butoxide, then the mixture was stirred for 2 hours at 140°C. After the reaction mixture was cooled to the room temperature, the mixture was condensed under reduced pressure and water was added to the residue. Further added 21mL of 1N-HCl to the mixture, the mixture was extracted with chloroform. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 100/1), and resultant product was further purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1) and recrystallized from ethyl acetate to give 1.12g (30%) of the title compound.

Example 15:

3-Cyclohexyl-6-{2-methoxy-6-[(4-methylphenyl)surfonyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound 1.02g (87%) was obtained in a manner similar to the Example 9 by using the compound obtained in the Example 14, instead of the compound obtained in the Example 8.

Example 16:

1-Cyclohexyl-5-[2-methoxy-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a solution of 134μL (1.22mmol) of N-methylpiperazine in 5mL of tetrahyrofuran was added by dripping 779μL of n-butyllithium in hexane

solution (1.56M hexane solution: 1.22mmol) at -30°C, and the mixture was stirred for 15 minutes at the same temperature. Then, to this mixture was added the compound obtained in the Example 9 at -30°C, and the mixture was stirred for 15 minutes. After adding water to the mixture and the temperature of the reaction mixture was raised to the room temperature, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 30/1) to give 123mg (93%) of the title compound.

Example 17:
1-Cyclohexyl-5-[2-methoxy-6-(4-morpholinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 72mg (56%) was obtained in a manner similar to the Example 16 using morpholine, instead of N-methylpiperazine.

Example 18:
1-Cyclohexyl-5-[2-methoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 16mg (12%) was obtained in a manner similar to the Example 16 by using N-methyl-homopiperazine, instead of N-methylpiperazine.

Example 19:
1-Cyclohexyl-5-(2-methoxy-3-pyridinyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a solution of 200mg (0.90mmol) of the compound obtained in the Example 6 in 3mL of dichloromethane were added to 165mg (1.08mmol) of 2-methoxynicotinic acid and 207mg (1.08mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture was stirred for over night at room temperature. After adding saturated sodium hydrogen carbonate aqueous solution, the mixture was extracted with dichloromethane.

The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, then, 6mL of ethanol and 3mL of sodium hydroxide aqueous solution were added to the residue, and the mixture was refluxed for 9 hours. After the reaction mixture was cooled to the room temperature, water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=2/1). The obtained product was recrystallized from the mixture solvent of ethyl acetate-hexane to give 78mg (26%) of the title compound.

Example 20:

3-Cyclohexyl-6-[2-methoxy-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound 86mg (65%) was obtained in a manner similar to the Example 16 using the compound obtained in the Example 15, instead of the compound obtained in the Example 9.

Example 21:

3-Cyclohexyl-6-[2-methoxy-6-(4-morpholinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound 58mg (45%) was obtained in a manner similar to the Example 16 using morpholine and the compound obtained in the Example 15, instead of N-methylpiperazine and the compound obtained in the Example 9, respectively.

Example 22:

3-Cyclohexyl-6-[2-methoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound 115mg (84%) was obtained in a manner similar to the Example 16 using N-methyl-homopirerazine and the compound obtained

in the Example 15, instead of N-methylpiperazine and the compound obtained in the Example 9, respectively.

Example 23:

3-Cyclohexyl-6-[6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methoxy-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound 776mg (quantitative) was obtained in a manner similar to the Example 16 using 1,4-dioxa-8-azaspiro[4.5]decane and the compound obtained in the Example 15, instead of N-methylpiperazine and the compound obtained in the Example 9, respectively.

Example 24:

3-Cyclohexyl-6-[2-methoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a suspension of 743mg (1.55mmol) of the compound obtained in the Example 23 in 30mL of acetone and 3mL of water was added 353mg (1.86mmol) of p-toluenesulfonic acid hydrate, and the mixture was refluxed for 5 hours. After the reaction mixture was cooled to the room temperature, the solvent was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from mixture solvent of ethyl acetate-ethanol to give 405mg (93%) of the title compound.

Example 25:

3-Cyclohexyl-6-[6-(4-hydroxy-1-piperidinyl)-2-methoxy-3-pyridinyl]-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a suspension of 120mg (0.28mmol) of the compound obtained in the Example 24 in 3mL of methanol was added 12.5mg (0.33mmol) of sodium borohydride, and the mixture was stirred for 2.5 hours at room temperature. Then, acetone was added to the reaction mixture and the solvent was removed

under reduced pressure. Water was added to the residue and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/ethyl acetate = 2/1 to 1/2), and the obtained crude product was recrystallized from ethanol to give 85mg (70%) of the title compound.

Example 26:

3-Cyclohexyl-6-{2-methoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one

To a suspension of 120mg (0.28mmol) of the compound obtained in the Example 24 in 2mL of 1,2-dichloromethane were added to 57μM (30% ethanol solution; 0.55mmol) of methylamine, 10μM of acetic acid and 87mg (0.41mmol) of sodium triacetoxyborohydride, and the mixture was stirred for 2 hours at room temperature. Then, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/ethyl acetate/methanol = 10/10/1). The obtained crude product was recrystallized from the mixture solvent of ethyl acetate-hexane to give 87mg (70%) of the title compound.

Example 27:

3-Cyclohexyl-6-{6-[4-(dimethylamino)-1-piperidinyl]-2-methoxy-3-pyridinyl}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one

The title compound 103mg (80%) was obtained in a manner similar to the Example 26 using dimethylamine、 instead of methylamine.

Example 28:

6-[6-(4-Amino-1-piperidinyl)-2-methoxy-3-pyridinyl]-3-cyclohexyl-

1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a mixture of 240mg (0.55mmol) of the compound obtained in the Example 24 in 10mL of 4M-ammnonia-etanol solution was added 24mg of 5% palladium-carbon and the mixture was stirred for 24 hours under hydrogen gas atmosphere at normal pressures. After the reaction, the mixture was filtrated by Celite® and filtrate was removed under reduced pressure. The resulting residue was purified by alkaline silica gel column chromatography (eluent: dichloromethane/ethyl acetate/methanol = 10/10/1) and obtained crude product was recrystallized from ethanol to give 169mg (70%) of the title compound.

Example 29:

N-{1-[5-(3-Cyclohexyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]-pyrimidin-6-yl)-6-methoxy-2-piridinyl]-4-piperidinyl}acetamide

To a solution of 80mg (0.18mmol) of the compound obtained in the Example 28 in 2mL of dichloromethane were added 21μL (0.22mmol) of acetic anhydride and 38μL of triethylamine, and the mixture was stirred for 1.5 hours at room temperature. Then, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give 79mg (90%) of the title compound.

Example 30:

1-Cyclohexyl-5-[6-(1,4-dioxa-8-axaspiro[4.5]dec-8-yl)-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 588mg (86%) was obtained in a manner similar to the Example 16 using 1,4-dioxa-8-axaspiro[4.5]decane instead of N-methylpiperazine.

Example 31:

1-Cyclohexyl-5-[2-methoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-

3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one

The title compound 255mg (50%) was obtained in a manner similar to the Example 24 using the compound obtained in the Example 30 instead of the compound obtained in the Example 23.

Example 32:

1-Cyclohexyl-5-{2-methoxy-6-[(4-(methylamino)-1-piperidinyl)-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one

The title compound 68mg (55%) was obtained in a manner similar to the Example 26 using the compound obtained in the Example 31 instead of the compound obtained in the Example 24.

Example 33:

1-Cyclohexyl-5-{-6-[4-(dimethylamino)-1-piperidinyl]-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one

The title compound 102mg (94%) was obtained in a manner similar to the Example 26 using the compound obtained in the Example 31 and dimethylamine instead of the compound obtained in the Example 24 and methylamine, respectively.

Example 34:

3-Cyclohexyl-6-(2-methoxy-6-sulfanyl-3-piridinyl)-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one

To a suspension of 230mg (0.47mmol) of the compound obtained in the Example 15 in 5mL of methanol was added 100mg of sodium hydrosulfide, and the mixture was refluxed for 4 hours. After cooling, 1M-HCl was added to the reaction mixture and the precipitate was collected. The obtained solid was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 20/1) to give 132mg (76%) of the title compound.

Example 35:

5-(3-Cyclohexyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo-[3,4-d]pyrimidin-6-yl)-6-methoxy-2-pyridinesulfonyl chloride

To a suspension of 120mg (0.32mmol) of the compound obtained in the Example 34 in 3mL of acetonitrile was added 82mg (0.81mmol) of potassium nitrate and to this mixture was added 65µL (0.81mmol) of sulfuryl chloride at 0°C. The mixture was stirred for 2 hours at room temperature, then, water was added to the reaction mixture. The precipitate was collected to give 114mg (81%) of the title compound.

Example 36:

3-Cyclohexyl-6-{2-methoxy-6-[(4-methyl-1,4-diazepan-1-yl)sulfony]-3-pyridiny}-1-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a solution of 104mg (0.24mmol) of the compound obtained in the Example 35 in 2mL of dichloromethane were added 35µL (0.29mmol) of N-methyl-homopiperazine and 83µL (0.59mmol) of triethylamine, and the mixture was stirred for 1 hour at room temperature. Then, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by alkaline silica gel column chromatography (eluent: ethyl acetate). The obtained crude solid was recrystallized from ethyl acetate-hexane to give 68mg (56%) of the title compound.

Example 37:

1-Cyclohexyl-5-[6-(4-hydroxy-1-piperidinyl)-2-methoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 73mg (60%) was obtained in a manner similar to the Example 25 using the compound obtained in the Example 31 instead of the compound obtained in the Example 24.

Example 38:

1-Cyclohexyl-5-{2-methoxy-6-[(4-methylphenyl)sulfinyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a solution of 1.5g (3.25mmol) of the compound obtained in the

Example 8 in 30mL of dichloromethane was added 701mg (3.25mmol) of m-chloroperbenzoic acid at 0°C, and the mixture was stirred for 40 minutes. Then, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. After the solvent was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was recrystallized from 2-butanone to give 1.0g (64%) of the title compound.

Example 39:

Ethyl 2-ethoxy-6-[(4-methylphenyl)sulfanyl]nicotinate

To a solution of 11.5g (92.4mmol) in 55mL of N,N-dimethylformamide was added 10.8g (96.0mmol) of potassium tert-butoxide at 0°C, and the mixture was stirred for 15 minutes at room temperature. This mixture was added by dripping to a solution of 19.56g (88.9mmol) of ethyl 2,6-dichloronicotinate in 150mL of N,N-dimethylformamide at -30°C for 15 minutes, and the mixture was stirred for 1 hour at the same temperature. Then, the reaction mixture was poured into ice water and extracted with a mixture solution of ethyl acetate/hexane (2/1). The organic layer was washed with water and saturated saline solution, then, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give ethyl 2-chloro-6-[(4-methylphenyl)sulfanyl]nicotinate intermediate as pale brown oil.

Then, this compound was dissolved in 180mL of tetrahydrofuran and 31.4g (92.4mmol) of 20% sodium ethoxide-ethanol solution was added to this solution, and the mixture was refluxed for 2 hours. After the reaction mixture was cooled to the room temperature, the mixture was filtrated, and the filtrate was removed under reduced pressure. The residue was diluted with chloroform and the organic layer was washed with water and saturated saline solution, then, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 5/1) to give 23.4g (83%) of the title compound.

Example 40:

2-Ethoxy-6-[(4-methylphenyl)sulfanyl]nicotinic acid

The title compound 20.16g (97%) was obtained in a manner similar to the Example 7 using the compound obtained in the Example 39 instead of methyl 2-methoxy-6-(4-methylbenzylthio)pyridine-3-carboxylate.

Example 41:

1-Cyclohexyl-5-{2-ethoxy-6-[(4-methylphenyl)sulfanyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a suspension of 3.18g (11mmol) of the compound obtained in the Example 40 in 30mL of 1,2-dichloromethane was added 1.60mL of thionyl chloride, and the mixture was refluxed for 2 hours. Then, the reaction mixture was cooled to the room temperature and the solvent was removed under reduced pressure to give the corresponding acid chloride as pale yellow solid. Then, this acid chloride was dissolved in 30mL of dichloromethane and to this solution were added 3.48mL (25mmol) of triethylamine, 2.22g (10mmol) of the compound obtained in the Example 6, and 50mL of dichloromethane, and then, the mixture was stirred for 2 hours at room temperature. Saturated sodium hydrogen carbonate aqueous solution was added the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water and saturates saline solution, dried over anhydrous sodium sulfate, and removed under reduced pressure to give the corresponding amide compound as intermediate. Then, this amide compound was suspended in 100mL of ethanol and to this suspension was added 2.81g (25mmol) of potassium tert-butoxide, and the mixture was refluxed for 14 hours. After the reaction mixture was cooled to the room temperature, the solvent was removed under reduced pressure. The residue was diluted with water and 20mL of 2N-HCl was added, and extracted with dichloromethane. The organic layer was washed with water and saturated saline solution, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: dichloromethane/ hexane/ethyl acetate = 10/20/1 to 10/10/1) to give 3.48g (73%) of the title compound.

Example 42:

1-Cyclohexyl-5-{2-ethoxy-6-[(4-methylphenyl)sulfonyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 2.97g (93%) was obtained in a manner similar to the Example 9 using the compound obtained in the Example 41 instead of the compound obtained in the Example 8.

Example 43:

1-Cyclohexyl-5-[2-ethoxy-6-[(4-methyl-piperazinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 131mg (98%) was obtained in a manner similar to the Example 16 using the compound obtained in the Example 42 instead of the compound obtained in the Example 9.

Example 44:

1-Cyclohexyl-5-[2-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 128mg (93%) was obtained in a manner similar to the Example 16 using N-methylhomopiperazine and the compound obtained in the Example 42, instead of N-methylpiperazine and the compound obtained in the Example 9, respectively.

Example 45:

1-Cyclohexyl-5-[6-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-ethoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 934mg (96%) was obtained in a manner similar to the Example 16 using 1,4-dioxa-8-azaspiro[4.5]decane and the compound obtained in the Example 42, instead of N-methylpiperazine and the compound obtained in the Example 9, respectively.

Example 46:

1-Cyclohexyl-5-[2-ethoxy-6-(4-oxo-1-piperidinyl)-3-pyridinyl]-3-

methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 791mg (97%) was obtained in a manner similar to the Example 24 using the compound obtained in the Example 45 instead of the compound obtained in the Example 23.

Example 47:

1-Cyclohexyl-5-{6-[4-(dimethylamino)-1-piperidinyl]-2-ethoxy-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 122mg (86%) was obtained in a manner similar to the Example 26 using dimethylamine and the compound obtained in the Example 46, instead of methylamine and the compound obtained in the Example 24, respectively.

Example 48:

1-Cyclohexyl-5-{2-ethoxy-6-[4-(methylamino)-1-piperidinyl]-3-pyridinyl}-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 103mg (83%) was obtained in a manner similar to the Example 26 by using the compound obtained in the Example 46 instead of the compound obtained in the Example 24.

Example 49:

1-Cyclohexyl-5-[2-ethoxy-6-(4-hydroxy-1-piperidinyl)-3-pyridinyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound 92mg (76%) was obtained in a manner similar to the Example 25 using the compound obtained in the Example 46 instead of the compound obtained in the Example 24.

Physicochemical data of the compounds obtained by the above-mentioned examples are summarized in the following Tables.

Table 1:

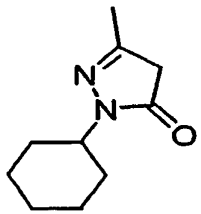
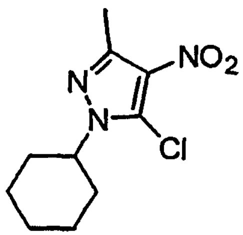
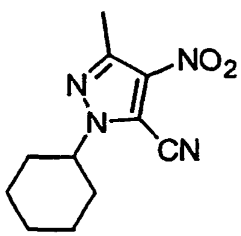
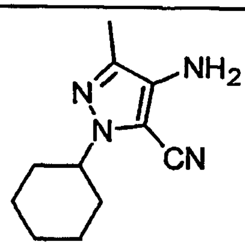
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
1		colorless solid 147.6–150.4	$CDCl_3$ 1.21–1.36(1H, m), 1.39–1.52(2H, m), 1.71–1.98(7H, m), 2.09(3H, s), 3.20(2H, s), 3.95–4.02(1H, m)	181
2		colorless solid 104.8–105.2 (hexane)	$CDCl_3$ 1.22–1.50(3H, m), 1.70–1.79(1H, m), 1.88–2.01(6H, m), 2.54(3H, s), 4.23–4.33(1H, m)	244
3		colorless solid 109.0–110.2 (hexane/AcOEt)	$CDCl_3$ 1.22–1.37(1H, m), 1.39–1.54(2H, m), 1.72–1.82(1H, m), 1.91–2.10(6H, m), 2.58(3H, s), 4.32–4.43(1H, m)	235
4		pale yellow solid 85.5–87.0 (hexane)	$CDCl_3$ 1.18–1.31(1H, m), 1.32–1.48(2H, m), 1.66–1.75(1H, m), 1.79–2.03(6H, m), 2.16(3H, s), 3.33(2H, brs), 4.02–4.14(1H, m)	205

Table 2:

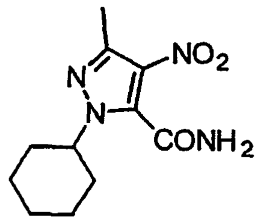
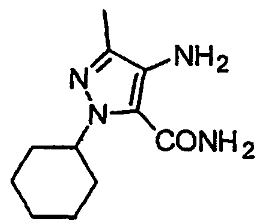
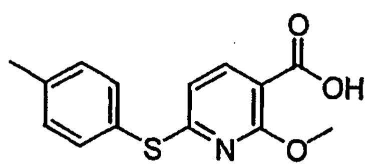
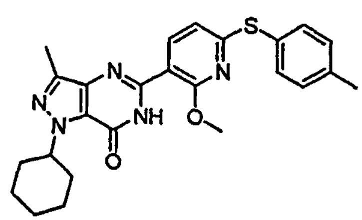
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
5		colorless solid 148.1–149.0 (AcOEt/hexane)	$CDCl_3$ 1.19–1.48(3H, m), 1.64–1.77(1H, m), 1.84–2.07(6H, m), 2.52(3H, s), 4.41–4.54(1H, m), 6.04(1H, brs), 6.77(1H, brs)	253
6		colorless solid 193–194 (AcOEt)	$CDCl_3$ 1.18–1.31(1H, m), 1.38–1.52(2H, m), 1.63–1.74(1H, m), 1.79–2.01(6H, m), 2.21(3H, s), 2.80(2H, s), 5.18–5.29(1H, m)	223
7		colorless solid 174–175	$CDCl_3$ 2.41(3H, s), 4.03(3H, s), 6.58(1H, d, J=8.1Hz), 7.26–7.31(2H, m), 7.46–7.51(2H, m), 8.14(1H, d, J=8.1Hz)	276
8		colorless solid 165–168	$CDCl_3$ 1.21–1.35(1H, m), 1.40–1.52(2H, m), 1.65–1.74(1H, m), 1.83–2.06(6H, m), 2.41(3H, s), 2.47(3H, s), 4.02(3H, s), 4.95–5.05(1H, m), 6.64(1H, d, J=8.3Hz), 7.23–7.27(2H, m), 7.47–7.51(2H, m), 8.56(1H, d, J=8.3Hz), 10.72(1H, brs)	462

Table 3:

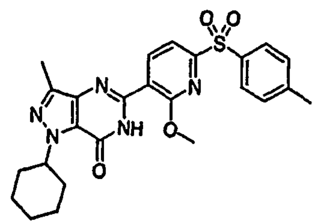
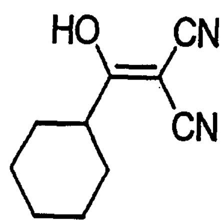
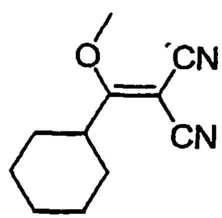
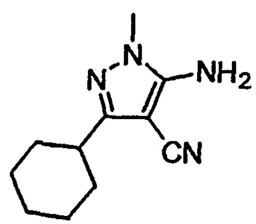
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
9		colorless solid 213–215	$CDCl_3$ 1.21–1.34(1H, m), 1.40–1.53(2H, m), 1.67–1.75(1H, m), 1.83–2.06(6H, m), 2.43(3H, s), 2.53(3H, s), 4.11(3H, s), 4.95–5.05(1H, m), 7.31–7.36(2H, m), 7.91–7.97(3H, m), 8.99(1H, d, J=8.0Hz), 10.63(1H, brs)	494
10		pale yellow solid 124–129 (di–isopropyl ethr)	$CDCl_3$ 1.12–1.41(3H, m), 1.45–1.58(2H, m), 1.68–1.89(5H, m), 2.77–2.86(1H, m)	177
11		pale yellow solid 58–59	$CDCl_3$ 1.12–1.51(5H, m), 1.66–1.85(5H, m), 2.77–2.86(1H, m), 4.34(1H, s)	191
12		colorless solid 139–141	$CDCl_3$ 1.20–1.41(3H, m), 1.48–1.62(2H, m), 1.65–1.73(1H, m), 1.77–1.85(2H, m), 1.88–1.97(2H, m), 2.57–2.66(1H, m), 3.58(3H, s), 4.13(2H, br–s)	205

Table 4:

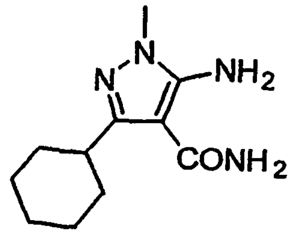
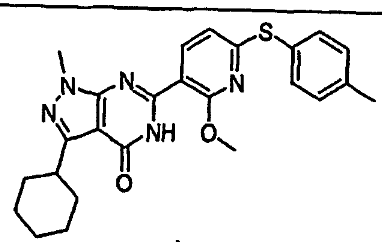
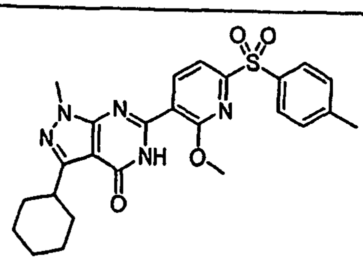
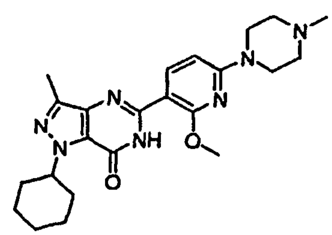
Example No.	Chemical Strucure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^{+}$
13		colorless solid 172–173.5	$CDCl_3$ 1.20–1.40(3H, m), 1.52–1.66(2H, m), 1.71–1.78(1H, m), 1.83–1.92(2H, m), 1.98–2.06(2H, m), 2.54–2.63(1H, m), 3.56(3H, s), 5.30(2H, br–s), 5.41(2H, br–s)	223
14		colorless solid 181–183 (AcOEt)	$CDCl_3$ 1.27–1.49(3H, m), 1.67–1.87(5H, m), 1.94–2.02(2H, m), 2.41(3H, s), 3.01–3.12(1H, m), 3.90(3H, s), 4.02(3H, s), 6.65(1H, d, J=8.2Hz), 7.22–7.29(2H, m), 7.47–7.53(2H, m), 8.58(1H, d, J=8.2Hz), 10.62(1H, brs)	462
15		colorless solid 215–216.5	$CDCl_3$ 1.22–1.50(3H, m), 1.66–1.88(5H, m), 1.93–2.04(2H, m), 2.44(3H, s), 3.01–3.11(1H, m), 3.97(3H, s), 4.11(3H, s), 7.31–7.39(2H, m), 7.91–8.00(3H, m), 9.41(1H, d, J=7.9Hz), 10.50(1H, brs)	494
16		pale yellow solid 213–215	$CDCl_3$ 1.21–1.36(1H, m), 1.41–1.59(2H, m), 1.67–1.76(1H, m), 1.84–2.09(6H, m), 2.35(3H, s), 2.48–2.55(7H, s), 3.65–3.70(4H, m), 4.09(3H, s), 4.95–5.05(1H, m), 6.34(1H, d, J=8.7Hz), 8.58(1H, d, J=8.7Hz), 10.81(1H, brs)	438

Table 5:

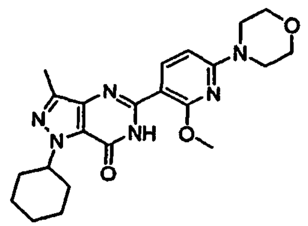
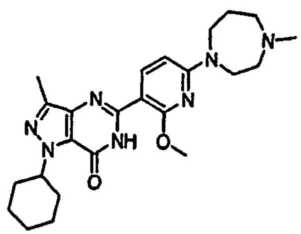
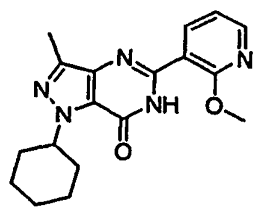
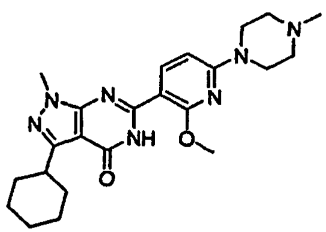
Example No.	Chemicla Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
17		colorless solid 220–223	CDCl $_3$ 1.22–1.35(1H, m), 1.41–1.57(2H, m), 1.67–1.75(1H, m), 1.84–2.08(6H, m), 2.52(3H, s), 3.59–3.64(4H, s), 3.80–3.85(4H, m), 4.09(3H, s), 4.95–5.05(1H, m), 6.34(1H, d, J=8.7Hz), 8.61(1H, d, J=8.7Hz), 10.80(1H, brs)	425
18		colorless solid 135–138	CDCl $_3$ 1.22–1.36(1H, m), 1.41–1.57(2H, m), 1.67–1.75(1H, m), 1.84–2.07(8H, m), 2.39(3H, s), 2.51(3H, s), 2.54–2.59(2H, s), 2.70–2.75(2H, m), 3.65–3.72(2H, m), 3.81–3.88(2H, m), 4.08(3H, s), 4.94–5.04(1H, m), 6.23(1H, d, J=8.7Hz), 8.55(1H, d, J=8.7Hz), 10.82(1H, brs)	452
19		colorless solid 172–174 (AcOEt/hexane)	CDCl $_3$ 1.21–1.38(1H, m), 1.44–1.58(2H, m), 1.68–1.79(1H, m), 1.85–2.09(6H, m), 2.55(3H, s), 4.19(3H, s), 4.98–5.09(1H, m), 7.13(1H, dd, J=4.9 and 7.7Hz), 8.31(1H, dd, J=1.9 and 4.9Hz), 8.83(1H, dd, J=1.9 and 7.7Hz), 10.86(1H, brs)	340
20		colorless solid 229.5–232 (EtOH)	CDCl $_3$ 1.26–1.51(3H, m), 1.68–1.87(5H, m), 1.95–2.03(2H, m), 2.35(3H, s), 2.46–2.54(4H, m), 3.01–3.11(1H, m), 3.64–3.74(4H, m), 3.92(3H, s), 4.09(3H, s), 6.35(1H, d, J=8.8Hz), 8.59(1H, d, J=8.8Hz), 10.65(1H, brs)	438

Table 6:

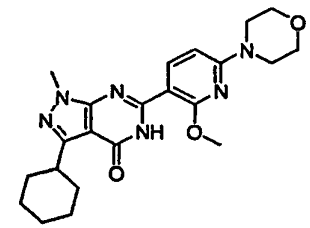
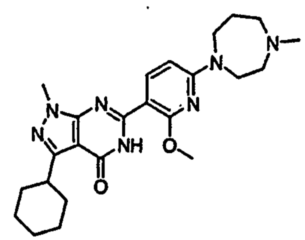
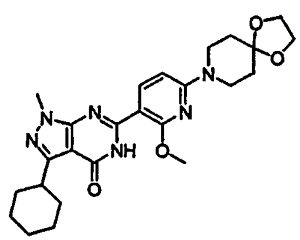
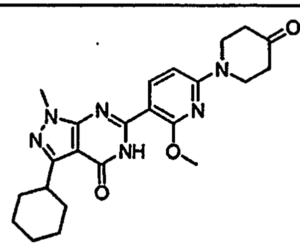
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
21		green/yellow solid 251.5–255 (EtOH)	$CDCl_3$ 1.26–1.51(3H, m), 1.69–1.88(5H, m), 1.96–2.04(2H, m), 3.01–3.11(1H, m), 3.60–3.69(4H, m), 3.78–3.86(4H, m), 3.92(3H, s), 4.09(3H, s), 6.34(1H, d, J=8.7Hz), 8.62(1H, d, J=8.7Hz), 10.64(1H, brs)	425
22		colorless solid 179.5–180.5	$CDCl_3$ 1.28–1.51(3H, m), 1.68–1.87(5H, m), 1.96–2.09(4H, m), 2.39(3H, s), 2.52–2.61(2H, m), 2.69–2.79(2H, m), 3.01–3.11(1H, m), 3.63–3.77(2H, m), 3.80–3.96(2H, m), 3.91(3H, s), 4.08(3H, s), 6.24(1H, d, J=8.7Hz), 8.57(1H, d, J=8.7Hz), 10.65(1H, brs)	452
23		colorless solid 232.5–234	$CDCl_3$ 1.28–1.50(3H, m), 1.69–1.89(9H, m), 1.95–2.05(2H, m), 3.01–3.11(1H, m), 3.73–3.83(4H, m), 3.92(3H, s), 4.00(4H, s), 4.08(3H, s), 6.39(1H, d, J=8.9Hz), 8.58(1H, d, J=8.9Hz), 10.65(1H, brs)	481
24		colorless solid 284–286 (AcOEt/EtOH)	$CDCl_3$ 1.28–1.51(3H, m), 1.68–1.88(5H, m), 1.96–2.05(2H, m), 2.53–2.62(4H, m), 3.01–3.11(1H, m), 3.93(3H, s), 3.98–4.07(4H, m), 4.12(3H, s), 6.45(1H, d, J=8.8Hz), 8.66(1H, d, J=8.8Hz), 10.62(1H, brs)	437

Table 7:

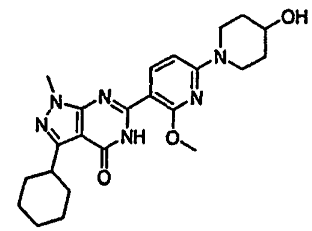
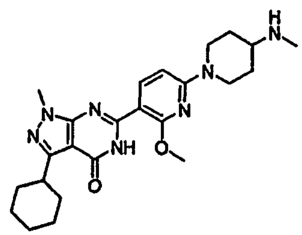
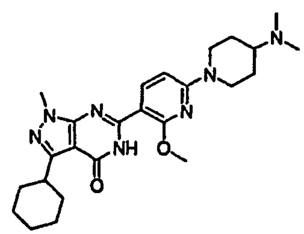
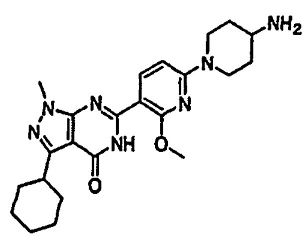
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
25		colorless solid 205–206.5 (EtOH)	$CDCl_3$ 1.28–1.50(3H, m), 1.53–1.65(2H, m), 1.69–1.88(5H, m), 1.94–2.04(4H, m), 3.00–3.10(1H, m), 3.30–3.40(2H, m), 3.92(3H, s), 3.94–4.03(1H, m), 4.06–4.17(2H, m), 4.09(3H, s), 6.38(1H, d, J=8.8Hz), 8.58(1H, d, J=8.8Hz), 10.65(1H, brs)	439
26		colorless solid 202–203.5 (AcOEt/hexane)	$CDCl_3$ 1.28–1.63(5H, m), 1.68–1.87(5H, m), 1.93–2.03(4H, m), 2.47(3H, s), 2.60–2.71(1H, m), 3.00–3.13(3H, m), 3.91(3H, s), 4.08(3H, s), 4.29–4.39(2H, m), 6.36(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 10.66(1H, brs)	452
27		colorless solid 178.5–180 (EtOH)	$CDCl_3$ 1.28–1.58(5H, m), 1.68–1.88(5H, m), 1.90–2.03(4H, m), 2.30(6H, s), 2.38–2.48(1H, m), 2.91–3.11(3H, m), 3.91(3H, s), 4.08(3H, s), 4.40–4.50(2H, m), 6.36(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 10.65(1H, brs)	466
28		colorless solid 206–208.5 (EtOH)	$CDCl_3$ 1.27–1.66(5H, m), 1.69–1.87(5H, m), 1.90–2.04(4H, m), 2.93–3.11(4H, m), 3.92(3H, s), 4.03(3H, s), 4.31–4.40(2H, m), 6.37(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 10.65(1H, brs)	438

Table 8:

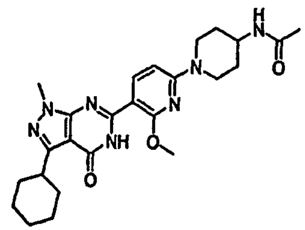
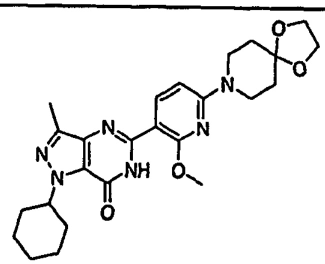
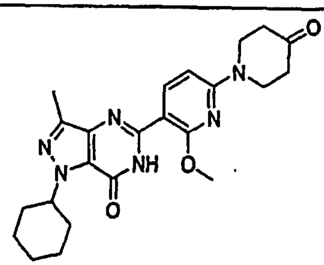
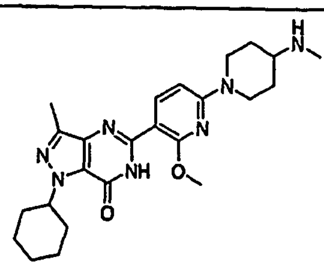
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
29		colorless solid 253.5–255.5 (EtOH)	$CDCl_3$ 1.24–1.50(5H, m), 1.69–1.88(5H, m), 1.94–2.11(4H, m), 1.98(3H, s), 3.01–3.15(3H, m), 3.92(3H, s), 4.01–4.14(1H, m), 4.08(3H, s), 4.33–4.42(2H, m), 5.30–5.39(1H, m), 6.37(1H, d, J=8.8Hz), 8.58(1H, d, J=8.8Hz), 10.63(1H, brs)	480
30		pale yellow solid 230–232	$CDCl_3$ 1.21–1.36(1H, m), 1.41–1.56(2H, m), 1.65–1.80(5H, m), 1.84–2.06(6H, m), 2.51(3H, s), 3.75–3.80(4H, m), 4.00(4H, s), 4.08(3H, s), 4.94–5.04(1H, m), 6.38(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 10.81(1H, brs)	481
31		colorless solid 277–278 (AcOEt/EtOH)	$CDCl_3$ 1.22–1.36(1H, m), 1.42–1.56(2H, m), 1.69–1.77(1H, m), 1.85–2.10(6H, m), 2.52(3H, s), 2.55–2.61(4H, m), 3.97–4.03(4H, m), 4.12(3H, s), 4.94–5.04(1H, m), 6.45(1H, d, J=8.7Hz), 8.66(1H, d, J=8.7Hz), 10.77(1H, brs)	437
32		colorless solid 185–189 (AcOEt/ diisopropyl ether)	$CDCl_3$ 1.20–1.42(5H, m), 1.66–1.74(1H, m), 1.83–2.06(8H, m), 2.47(3H, s), 2.51(3H, s), 2.60–2.69(1H, m), 3.00–3.09(2H, m), 4.08(3H, s), 4.28–4.36(2H, m), 4.94–5.04(1H, m), 6.36(1H, d, J=8.8Hz), 8.56(1H, d, J=8.8Hz), 10.82(1H, brs)	452

Table 9:

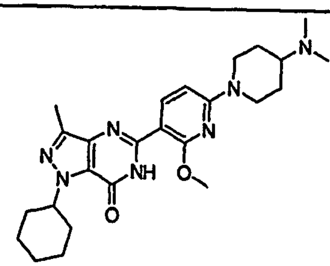
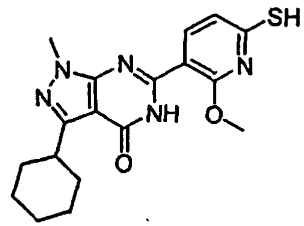
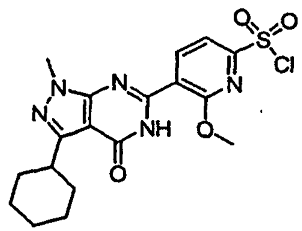
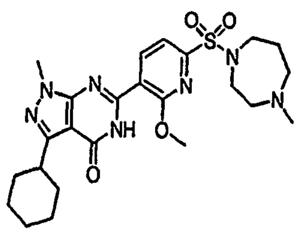
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
33		colorless solid 230–231 (EtOH/AcOEt)	$CDCl_3$ 1.22–1.36(1H, m), 1.42–1.58(4H, m), 1.66–1.75(1H, m), 1.83–2.08(8H, m), 2.30(6H, s), 2.36–2.46(1H, m), 2.51(3H, s), 2.89–2.99(2H, m), 4.08(3H, s), 4.39–4.48(2H, m), 4.95–5.05(1H, m), 6.36(1H, d, J=8.8Hz), 8.56(1H, d, J=8.8Hz), 10.82(1H, brs)	466
34		colorless solid 184(dec.)	$CDCl_3$ 1.28–1.51(3H, m), 1.69–1.91(5H, m), 1.98–2.09(2H, m), 3.03–3.17(1H, m), 3.96(3H, s), 4.15(1H, s), 4.17(3H, s), 7.02(1H, d, J=8.1Hz), 8.65(1H, d, J=8.1Hz), 10.62(1H, brs)	372
35		pale yellow solid 229–232	$CDCl_3$ 1.28–1.52(3H, m), 1.68–1.90(5H, m), 1.98–2.06(2H, m), 3.04–3.15(1H, m), 3.99(3H, s), 4.33(3H, s), 7.87(1H, d, J=7.8Hz), 9.12(1H, d, J=7.8Hz), 10.54(1H, brs)	438
36		pale yellow solid 153.5–155.5 (AcOEt/hexane)	$CDCl_3$ 1.22–1.51(3H, m), 1.60–2.04(9H, m), 2.37(3H, s), 2.61–2.72(4H, m), 3.02–3.15(1H, m), 3.53–3.67(4H, m), 3.98(3H, s), 4.22(3H, s), 7.74(1H, d, J=7.8Hz), 9.00(1H, d, J=7.8Hz), 10.56(1H, brs)	516

Table 10:

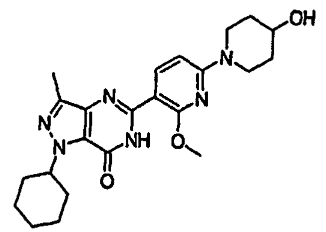
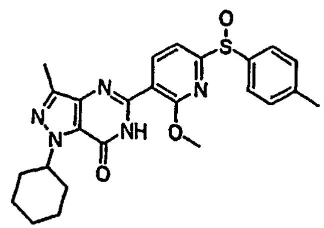
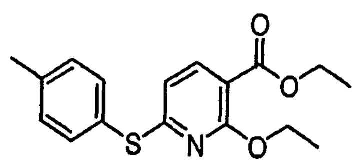
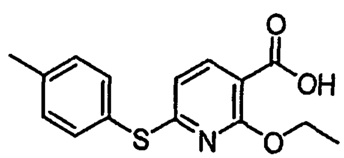
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
37		colorless solid 217–220	$CDCl_3$ 1.20–1.35(1H, m), 1.42–1.64(4H, m), 1.68–1.75(1H, m), 1.83–2.08(8H, m), 2.51(3H, s), 3.27–3.35(2H, m), 3.94–4.02(1H, m), 4.09(3H, s), 4.08–4.17(2H, m), 4.94–5.04(1H, m), 6.38(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 10.81(1H, brs)	439
38		colorless solid 231–233 (2–butanone)	$CDCl_3$ 1.21–1.34(1H, m), 1.41–1.57(2H, m), 1.69–1.76(1H, m), 1.85–2.06(6H, m), 2.37(3H, s), 2.52(3H, s), 4.11(3H, s), 4.95–5.06(1H, m), 7.27(2H, d, J=8.1Hz), 7.67(2H, d, J=8.1Hz), 7.84(1H, d, J=8.0Hz), 8.96(1H, d, J=8.0Hz), 10.59(1H, brs)	478
39		pale yellow oil	$CDCl_3$ 1.30(3H, t, J=7.1Hz), 1.32(3H, t, J=7.1Hz), 2.39(3H, s), 4.29(2H, q, J=7.1Hz), 4.32(2H, q, J=7.1Hz), 6.42(1H, d, J=8.1Hz), 7.19–7.29(2H, m), 7.43–7.52(2H, m), 7.91(1H, d, J=8.1Hz)	318
40		colorless solid 136.5–140	$CDCl_3$ 1.38(3H, t, J=7.1Hz), 2.41(3H, s), 4.49(2H, q, J=7.1Hz), 6.58(1H, d, J=8.1Hz), 7.22–7.30(2H, m), 7.43–7.50(2H, m), 8.14(1H, d, J=8.1Hz)	290

Table 11:

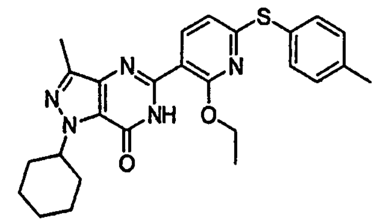
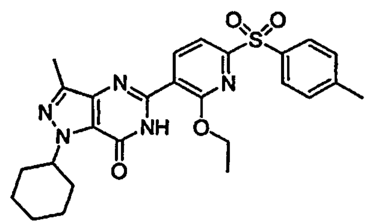
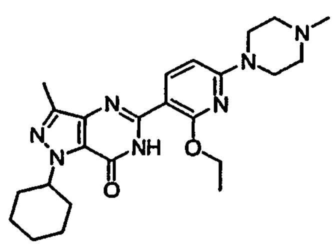
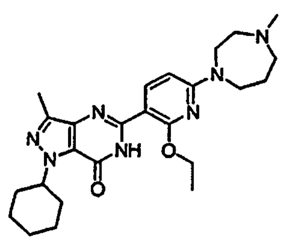
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
41		colorless solid 190–191 (EtOH)	$CDCl_3$ 1.20–1.35(1H, m), 1.39–1.52(2H, m), 1.42(3H, t, J=7.1Hz), 1.66–1.76(1H, m), 1.83–2.09(6H, m), 2.41(3H, s), 2.49(3H, s), 4.64(2H, q, J=7.1Hz), 4.92–5.02(1H, m), 6.63(1H, d, J=8.2Hz), 7.20–7.28(2H, m), 7.46–7.51(2H, m), 8.57(1H, d, J=8.2Hz), 10.93(1H, brs)	476
42		pale yellow solid 229–230 (EtOH)	$CDCl_3$ 1.21–1.36(1H, m), 1.40–1.52(2H, m), 1.46(3H, t, J=7.1Hz), 1.69–1.75(1H, m), 1.86–2.08(6H, m), 2.43(3H, s), 2.53(3H, s), 4.57(2H, q, J=7.1Hz), 4.94–5.03(1H, m), 7.31–7.38(2H, m), 7.9–7.99(3H, m), 9.00(1H, d, J=8.1Hz), 10.78(1H, brs)	508
43		colorless solid 162.5–163.5 (EtOH)	$CDCl_3$ 1.21–1.35(1H, m), 1.40–1.57(2H, m), 1.53(3H, t, J=7.1Hz), 1.67–1.75(1H, m), 1.83–2.09(6H, m), 2.34(3H, s), 2.45–2.57(4H, m), 2.51(3H, s), 3.60–3.71(4H, m), 4.56(2H, q, J=7.1Hz), 4.93–5.05(1H, m), 6.34(1H, d, J=8.8Hz), 8.59(1H, d, J=8.8Hz), 11.02(1H, brs)	452
44		colorless solid 151–152 (AcOEt/hexane)	$CDCl_3$ 1.21–1.36(1H, m), 1.40–1.58(2H, m), 1.52(3H, t, J=7.1Hz), 1.61–1.781H, m), 1.82–2.09(8H, m), 2.38(3H, s), 2.51(3H, s), 2.54–2.51(2H, s), 2.69–2.77(2H, m), 3.62–3.73(2H, m), 3.80–3.91(2H, m), 4.54(2H, q, J=7.1Hz), 4.92–5.06(1H, m), 6.22(1H, d, J=8.9Hz), 8.56(1H, d, J=8.9Hz), 11.02(1H, brs)	466

Table 12:

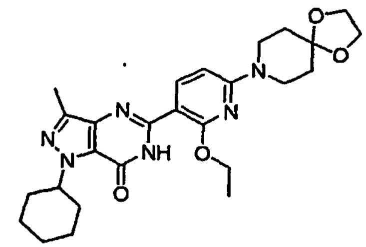
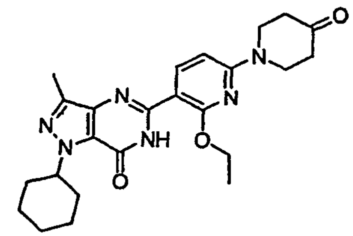
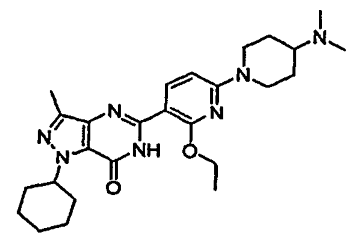
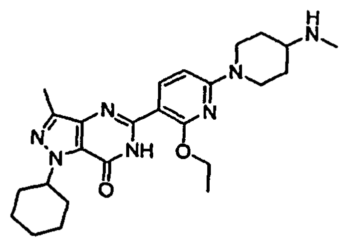
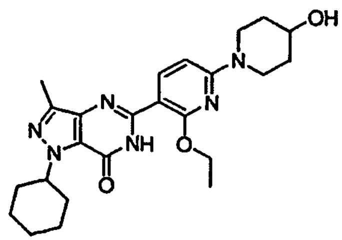
Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
45		colorless solid 166–167	$CDCl_3$ 1.22–1.38(1H, m), 1.41–1.56(2H, m), 1.52(3H, t, J=7.1Hz), 1.68–1.79(5H, m), 1.84–2.09(6H, m), 2.51(3H, s), 3.71–3.81(4H, m), 4.00(4H, s), 4.55(2H, q, J=7.1Hz), 4.92–5.04(1H, m), 6.38(1H, d, J=8.8Hz), 8.57(1H, d, J=8.8Hz), 11.01(1H, brs)	495
46		colorless solid 220–221 (AcOEt)	$CDCl_3$ 1.21–1.36(1H, m), 1.40–1.59(2H, m), 1.55(3H, t, J=7.1Hz), 1.67–1.79(1H, m), 1.84–2.10(6H, m), 2.52(3H, s), 2.53–2.61(4H, m), 3.94–4.04(4H, m), 4.58(2H, q, J=7.1Hz), 4.91–5.03(1H, m), 6.45(1H, d, J=8.7Hz), 8.66(1H, d, J=8.7Hz), 10.97(1H, brs)	451
47		colorless solid 186–186.5 (EtOH)	$CDCl_3$ 1.22–1.39(1H, m), 1.41–1.59(4H, m), 1.54(3H, t, J=7.1Hz), 1.68–1.77(1H, m), 1.85–2.10(8H, m), 2.31(6H, s), 2.35–2.49(1H, m), 2.53(3H, s), 2.89–3.00(2H, m), 4.38–4.49(2H, m), 4.57(2H, q, J=7.1Hz), 4.97–5.08(1H, m), 6.37(1H, d, J=8.8Hz), 8.58(1H, d, J=8.8Hz), 11.03(1H, brs)	480
48		colorless solid 155–156.5 (AcOEt/hexane)	$CDCl_3$ 1.22–1.62(5H, m), 1.54(3H, t, J=7.1Hz), 1.69–1.78(1H, m), 1.86–2.10(8H, m), 2.48(3H, s), 2.53(3H, s), 2.61–2.70(1H, m), 3.00–3.10(2H, m), 4.27–4.38(2H, m), 4.57(2H, q, J=7.1Hz), 4.96–5.08(1H, m), 6.37(1H, d, J=8.8Hz), 8.58(1H, d, J=8.8Hz), 11.04(1H, brs)	466

Table 13:

Example No.	Chemical Structure	Properties m.p.(℃) (recryst. solvent)	^{1}H-NMR	MS(FAB) $(M+1)^+$
49		colorless solid 198–199 (EtOH)	$CDCl_3$ 1.22–1.37(1H, m), 1.41–1.65(4H, m), 1.54(3H, t, J=7.1Hz), 1.68–1.78(1H, m), 1.86–2.10(8H, m), 2.53(3H, s), 3.26–3.37(2H, m), 3.94–4.03(1H, m), 4.07–4.16(2H, m), 4.57(2H, q, J=7.1Hz), 4.94–5.05(1H, m), 6.38(1H, d, J=8.8Hz), 8.59(1H, d, J=8.8Hz), 11.03(1H, brs)	453

Industrial Applicability

The compounds of the present invention inhibit PDE 7 selectively, and therefore, enhance cellular cAMP level. Consequently, the compounds of the present invention are useful for treating various kinds of disease such as allergic disease, inflammatory disease or immunologic disease.

That is, the compounds of the present invention are useful for treating or preventing the diseases such as bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease, allergic rhinitis, psoriasis, atopic dermatitis, conjunctivitis, osteoarthritis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, hepatitis, pancreatitis, encephalomyelitis, septicemia, Crohn's disease, rejection for organ transplantation, GVH disease, and restenosis after angioplasty.